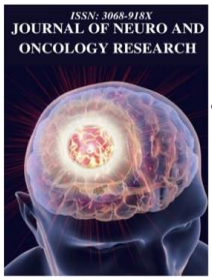

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Review Article

What's the Evidence Based on Healthy Super Agers?

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Abstract

As the global elderly population is projected to reach approximately 46.4% by 2070, with nations like South Korea rapidly transitioning into super-aged societies, research into age-related cognitive decline and resilience has grown increasingly critical. The concept of "Superagers," individuals aged 65 and older who maintain cognitive abilities comparable to those decades younger, offers a promising framework for investigating cognitive reserve and resilience against neurodegeneration.

Lee, et al., conducted a pioneering study aimed at identifying the biological underpinnings of Superager status using both traditional statistical analyses and advanced machine learning techniques. While conventional methods detected significant differences in only four biomarkers, machine learning-based feature selection expanded the biomarker panel to 15, indicating a more complex biological profile underlying exceptional cognitive aging.

Importantly, the study employed Shapley Additive Explanations (SHAP) to enhance model interpretability, demonstrating how specific blood-based biomarkers contribute to cognitive performance. These findings underscore the potential of using routine blood tests to not only assess cognitive function but also to predict and classify Superager status in healthy elderly populations. The study offers clinically significant insights and establishes a foundation for future explorations into the biological mechanisms that support cognitive resilience in aging populations.

Keywords: Shapley Additive Explanations; Superager; Biomarkers; Aging Populations

Introduction

Superagers exhibit exceptionally high cognitive performance for their age, often matching or exceeding that of individuals several decades younger. Superagers are clinically significant because they provide a unique model for understanding the contributing factors of healthy cognitive aging. Identifying and studying these individuals can offer insights into protective factors against cognitive decline and dementia, potentially guiding interventions to promote cognitive health in the broader elderly population. Superagers exhibit lower levels of metabolic inflammation, which may be a critical factor protecting them from age-associated cognitive decline.

Methodology

Literature review on Decoding cognitive aging: how white matter tracts and demographics distinguish potential Super Agers.

Predicting Superagers: A machine learning approach utilizing gut microbiome features, Machine learning based prediction of cognitive metrics using major biomarkers in Super-Agers, Superagers resist typical age-related white matter structural changes. characterization of African American Super-Agers in the National Alzheimer's Coordinating Center cohort. Is personality the key factor in becoming a Super Ager?) and evaluating the association of APOE genotype and cognitive resilience in SuperAgers. medRxiv.

Literature Analysis

Recent research highlights the distinct gut microbiome composition of superagers, older adults who maintain exceptional cognitive function, suggesting a potential biological basis for their resilience to age-related cognitive decline [1]. While cognitive impairment in aging populations, such as those with Mild Cognitive Impairment (MCI) or Alzheimer's Disease (AD), is often associated with complex neuropathological changes, superagers appear to defy this trajectory.

Diffusion Magnetic Resonance Imaging (dMRI) has been utilized to characterize these pathological changes, showing reduced Fractional Anisotropy (FA) and increased Mean Diffusivity (MD) in deep white matter regions like the centrum semiovale, indicating compromised white matter integrity in typical aging [1].

In contrast, superagers exhibit Superior performance in memory, visuospatial, language and executive functions [1]. A distinct gut microbiome profile, with increased abundance of beneficial microbial families and genera, including:
Lachnospiraceae, associated with youthful gut profiles.
Christensenellaceae, linked to lower inflammation, reduced adiposity and cognitive protection.
PAC001236_g (Mogibacterium family), unexpectedly linked to superagers despite previous associations with negative neurological outcomes.
Leuconostoc, a probiotic genus, is typically lower in MCI patients and potentially contributes to enhanced cognitive performance [1].
Intervention Implications: Evidence from related studies supports the potential of probiotic and prebiotic treatments to modulate microbiomes and preserve neurocognitive function in older adults. A notable example includes a 10-week multispecies probiotic intervention that improved cognition and mood in healthy older adults [1].

Fili, et al., present a comprehensive, multimodal framework to quantify and predict cognitive aging by integrating diffusion Magnetic Resonance Imaging (dMRI), demographic variables and baseline cognitive test results [2]. The study introduces several novel contributions to cognitive neuroscience and aging research, emphasizing explainable machine learning and longitudinal prediction of cognitive trajectories.

Key Findings by Fili, et al., [2]:
Education: Strongly associated with Positive-Ager status, confirming the cognitive reserve theory.
Age: Inversely correlated with positive aging; increasing age decreases the likelihood of being a Positive-Ager. Waist *Circumference:* Complex, age and sex-dependent associations: In women over 65, higher waist circumference was positively correlated with cognitive health. Suggested that adipose tissue may help compensate for postmenopausal estrogen reduction, a key hormonal link to cognitive protection. SHAP analysis revealed a significant interaction effect between sex and waist circumference.
Sex Differences: Men were more likely classified as Positive-Agers overall, though prior literature supports superior verbal and memory skills in women and better visuospatial abilities in men.
Neuroanatomical Imaging Biomarkers (dMRI): Fornix + Stria Terminalis: Lower MO (mode of anisotropy) values (< 0.45) were linked to a 7% reduced chance of positive aging. These regions play critical roles in memory and limbic processing. Supports literature linking fornix integrity to episodic memory and dementia risk.

Medial Lemniscus (Mean L1): Though not often studied in cognitive aging, reduced integrity in this sensorimotor tract has been associated with neurological impairments in various conditions.

Cerebral Peduncle (OD-Orientation Dispersion): Higher OD values (> 0.104) were predictive of a 2.5% lower likelihood of positive cognitive aging. Indicates microstructural degeneration in motor-cognitive networks.

Superagers (SAs) represent a rare subset of older adults whose cognitive performance remains on par with or surpasses that of individuals decades younger, effectively defying the normative patterns of age-related cognitive decline [1]. Batra, et al., study emphasizes a life course perspective, acknowledging that cognitive aging and functional integrity are shaped by the interplay of lifestyle, education, occupation, genetics, and, critically, personality traits.

Theoretical Foundation: Personality and Cognitive Aging

Batra, et al., are using the Big Five Personality Traits framework: Neuroticism, Conscientiousness, Extraversion, Agreeableness and Openness to Experience [3]. The study explores how stable personality dimensions may contribute to or hinder cognitive aging outcomes.

Neuroticism: Associated with increased stress, negative emotions and cognitive vulnerability. High neuroticism correlates with greater cognitive decline and higher rates of depression.

Conscientiousness: Tied to psychological well-being, self-discipline and goal-directed behavior. Predicts better cognitive outcomes and slower decline over time.

Extraversion: Linked to greater resilience, social engagement, autonomy and overall life satisfaction.

Agreeableness: Promotes adaptive coping, positive interpersonal interactions and emotional stability.

Openness to Experience: Associated with intellectual curiosity, experiential richness and longevity. Enhances life satisfaction and cognitive flexibility.

This study provides novel insight into the underexplored psychological dimensions of Superagers, particularly within the Indian population, where such analyses have previously been lacking. It suggests that personality traits are not merely byproducts of aging but may be determinants of aging trajectories [3]. Particularly, low neuroticism, high openness/conscientiousness profiles support superior cognitive aging trajectories. Trammell, et al., explored the demographic, behavioral and health characteristics that distinguish Superagers, older adults with exceptional cognitive performance, from their age-matched peers within an African American cohort. The study emphasizes modifiable lifestyle and health-related factors that may contribute to the preservation of cognition in aging individuals.

Super-agers were mostly female and more educated, had similar vascular comorbidities as the other groups and had fewer sleep disorders, depression and alcohol use. After adjusting for sex and education, the super-ager group assignment was associated with fewer sleep disorders, less depression and moderate alcohol use [4].

Lee, et al., present a biomarker-driven exploration of Superagers, older adults whose cognitive performance rivals individuals decades younger, despite normative aging processes [5]. This study identifies and categorizes 15 physiological blood biomarkers associated with Super Aging, proposing a biological framework for understanding cognitive resilience. Main Contributions: Identified 15 blood-based biomarkers associated with Super Ager status. Grouped biomarkers by physiological domains: glycemic regulation, lipid processing pathways, pro-inflammatory signaling, liver enzyme profile, electrolyte homeostasis and hematologic profile. Conducted threshold-based and domain-specific mapping to link biomarkers with distinct cognitive functions (e.g., memory, attention, visuospatial processing [5].

Lee, et al., found no significant difference in Alzheimer 's-related biomarkers (β-amyloid, tau) or inflammatory cytokine IL-6, suggesting Superagers' resilience is distinct from AD-pathology [5]. Proposed multimodal integration (e.g., MRI + biomarkers) as a future path for cognitive aging research. Lee, et al., indicated that Cognitive resilience is strongly associated with metabolic stability, particularly: Tightly regulated glucose and healthy lipid metabolism, Low oxidative stress (low oxLDL) and reduced systemic inflammation (low AGE/RAGE pathway activity) [5]. These biomarkers provide early indicators of cognitive well-being among the elderly, possibly before neurodegeneration becomes evident through β-amyloid or tau pathology. Super Agers exhibit lower levels of metabolic inflammation, which may be a critical factor protecting them from age-associated cognitive decline. The absence of differences in classical AD markers suggests that Super Agers' cognitive strength arises from systemic resilience rather than simply avoiding disease pathology. Garo-Pascual, et al., provide compelling evidence that Super Agers maintain superior memory performance into late life largely due to the preservation of white matter microstructure, particularly in regions of the brain most vulnerable to aging [6]. This study builds on prior gray matter analyses, reinforcing the view that structural integrity in both gray and white matter underpins the Super Aging phenotype.

White Matter Integrity as a Core Protective Mechanism: Superagers show better preserved white matter microstructure compared to typical older adults. This supports the theory that resistance to structural brain aging, rather than early developmental advantages, underlies their exceptional memory function [6]. Anterior Brain Regions and Vulnerable Tracts Are better preserved: White matter tracts in the anterior portion of the brain and those with late maturation (according to the last-in-first-out hypothesis), showed greater preservation in Superagers [6]. This suggests that Superagers resist age-related degeneration more effectively in areas most prone to deterioration [7].

Conclusion

The value of routine blood-based biomarkers for early identification of brain health in older populations at risk for cognitive decline. Preventative strategies could focus on metabolic optimization through diet and physical activity, blood sugar regulation and lipid profile management. The relationship between personality stability and cognitive resilience or decline in older age. The findings support the development of non-invasive, early screening tools based on simple cognitive tests and standard demographic data. Encourages future research into less-studied white matter tracts like the medial lemniscus and cerebral peduncle in cognitive decline. APOE-ε2 not only reduces the likelihood of dementia in the oldest age but also increases the likelihood that one will possess optimal memory in the oldest age.

Conflict of Interests

The authors have no conflict of interest to declare related to this article.

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